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The Office of Pollution Prevention and Toxics of the U.S. Environmental Protection Agency is to be commended for the thoughtful inclusion of pharmacokinetic analysis in the planning of toxicity testing for Hazardous Air Pollutants. This represents an important development in the ongoing efforts at EPA to more completely utilize mode of action and dosimetry data in hazard characterization and dose-response assessment for the risk assessment of chemicals (REF Cancer Guidelines).

Adequate toxicity testing for chemicals is critical for evaluating their potential impacts on human health. However, because toxicity testing can often be an expensive and time consuming process, it is important to avoid redundant, "square-filling" testing that generates limited useful information for risk assessment. The proposed test rule for the HAPs begins to address the issue of how to obtain data useful for risk assessment in a cost-effective manner.

A significant feature of the proposed test rule is the recognition that systemic toxicities arise from the biologically effective dose reaching the relevant tissue, regardless of the route. Differences in pharmacokinetics associated with the different exposure routes alter the doses reaching the tissue, not the efficacy of the tissue dose. By accounting for exposure route pharmacokinetics, it becomes unnecessary to test each chemical for every systemic endpoint by three exposure routes (i.e. oral, inhalation, dermal). The proposed rule also correctly identifies the need to determine whether portal-of-entry toxicity occurs, because when such effects occur, they are dependent upon the exposure route. Thus, hazard characterization and dose-response assessment for the three exposure routes can be obtained through a cost-effective combination of studies of dose route-specific pharmacokinetics and portal-of-entry effects (if any), and adequate systemic toxicity testing by a single route.

The proposal for route-to-route extrapolation laudable reflects the current emphasis in the toxicology and risk assessment communities recognizing the use of mode of action and dosimetry information for organizing scientific information in chemical risk assessment. We strongly support this direction. It offers opportunities to: 1) structure systematic incorporation of scientific data into chemical risk assessment, 2) reduce uncertainties associated with extrapolations to low doses, among species, and across dose routes and exposure regimens, and 3) strengthen the credibility of risk assessment by differentiating between scientifically-based extrapolation and policy judgements for risk management purposes. The use of quantitative pharmacokinetic extrapolations and qualitative mode of action information for guiding the process of route-to-route extrapolation represents an achievable and reasonable option for chemical risk assessment.

Sincerely,

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